



Docket No.: I0717.0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Fabrizio Samaritani et al.

Application No.: 10/009,380

Filed: April 1, 2002

Art Unit: 1647

For: GRF-CONTAINING LYOPHILIZED
PHARMACEUTICAL COMPOSITIONS

Examiner: R. M. Deberry

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This brief is filed in furtherance of the Notice of Appeal.

The fees required under § 41.20(b)(2), and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings:

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|------|-----------------------------------|
| I. | Real Party In Interest |
| II | Related Appeals and Interferences |
| III. | Status of Claims |
| IV. | Status of Amendments |
| V. | Summary of Invention |
| VI. | Issues |

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| VII. | Grouping of claims |
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I. REAL PARTY IN INTEREST

The real party in interest for this appeal is Applied Research System ARS Holding N.V.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A total of 15 claims were presented in this application. All are pending and all are the subject of this appeal. A copy of the claims involved in the present appeal is attached hereto as Appendix A.

IV. STATUS OF AMENDMENTS

Applicant did not amend the claims after Final Rejection.

V. SUMMARY OF INVENTION

Human growth hormone releasing factor, also known as GRF and somatostatin, is a naturally occurring, 44 amino acid peptide and also exists as 40 and 37 amino acid forms. All three forms are active for the diagnosis and treatment of growth hormone deficiency and related conditions.

The background section on pages 1-3 of the present application acknowledges that it is known that GRF requires stabilization. It identifies scientific literature which teaches that GRF suffers from chemical degradation in aqueous solution, primarily at the amino acid in the 8th position (Asn) and that the main hydrolytic reactions represent rearrangement of the amino acid (Asp) at the 3 position, cleavage of the bond between the 3 and 4 position amino acids (Asp and Ala), and deamination and rearrangement of the Asn amino acid at position 8. The application also points out that commercially available human GRF (hGRF) in lyophilized formulations is stabilized with mannitol.

The present invention is based on the discovery that saccharose can be used to stabilize GRF. The claims on appeal relate to a pharmaceutical composition which contains a solid intimate mixture of GRF and a stabilizing amount of saccharose or to a solution formed by reconstituting the solid mixture, and to a process of forming a lyophilizate.

VI. ISSUES

1. Should the rejection of Claims 1-3, 6-10 and 13 have been rejected under 35 USC § 103 over Fabbri (U.S. 5,017,557) in view of Samaritani (WO 95/35116) be reversed.

2. Should the rejection of Claims 1, 4, 5, 11 and 12 under 35 USC § 103 over Fabbri in view of Samaritani and Fujioka (U.S. 4,963,529) be reversed.

3. Should the rejection of Claims 1, 2 and 13-15 under 35 USC § 103 over Fabbri, Samaritani and Tarantino (U.S. 5,863,549) be reversed.

VII. GROUPING OF CLAIMS

All claims on appeal do not stand and fall together for the reasons set forth in the Argument section of this Brief.

VIII. ARGUMENT

GRF is a naturally occurring peptide which requires, whether in its 44, 40 or 37 amino acid forms, stabilization. The scientific literature identified in the application discloses that the chemical degradation of GRF in aqueous solution occurs primarily at the 8 position amino acid (Asn) and that the main hydrolytic reactions represent rearrangement of the amino acid at the 3 position (Asp), cleavage of the bond between the 3 and 4 position amino acids (Asp and Ala), and deamination and rearrangement of the Asn amino acid at position 8. The Fujioka reference also teaches that the amino acid at the 27 position (Met) requires stabilization. The application also acknowledges that commercially available human GRF in lyophilized formulations is stabilized with mannitol.

The present invention is based on the discovery that saccharose can surprisingly be used to stabilize GRF and provides a better stability profile than the

known stabilizer mannitol. Data demonstrating the superior results achieved are set forth in the application.

1. The Combination of Fabbri and Samaritani Does Not Render Claims 1-3, 6-10 And 13 Obvious

Claims 1-3, 6-10 and 13 have been rejected under 35 USC § 103 over Fabbri in view of Samaritani. These claims are directed to a pharmaceutical composition comprising a solid intimate mixture of GRF and a stabilizing amount of saccharose, alone or in combination with other excipients such as buffering agents, or a solution in which the solid mixture has been reconstituted in a solvent.

The primary reference, Fabbri, teaches nothing more than the fact that GRF exists. There is no reference to stabilization or even of any need for stabilization in this patent. It does not, as acknowledged by the Examiner, teach or suggest the use of saccharose in a GRF composition, or indeed in any pharmaceutical composition, for any purpose. In fact, Fabbri contains less relevant information than is set forth in the background section of the application on appeal.

To overcome this basic deficiency in the rejection, the Examiner has relied on Samaritani but that reference is explicitly limited to a different material, namely, human growth hormone (HGH). HGH is a linear polypeptide containing a chain of 191 amino acids and 2 interchange disulfide bridges (page 1, lines 9-14). In contrast, GRF is a small peptide which exists in 44, 40 or 37 amino acid chain forms with the activity residing mainly in the first 29 amino residues (application page 1, lines 12-14). The record is barren of any teaching or suggestion that these two very different materials are either subject to the same type of stability problems or that they can be stabilized in the same manner. Samaritani does not refer, even in passing, to stabilization of anything other than HGH.

Samaritani does teaches that saccharose can stabilize HGH but the reference does not teach or suggest that the saccharose can stabilize any other protein. Moreover, what requires stabilization in GRF is the amino acid Met at position 27, the amino acid Asp at position 3, the Asp - Ala bond at connecting positions 3-4 and the amino acid Asn at position 8 (application page 1, line 28 to page 2, line 7; Fujioka column 1, lines 43-44). Obviousness is a conclusion which must have a factual basis, *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed Cir. 2002) (“common knowledge” and “common sense” not a substitute for evidence); *Ex Parte Haymond*, 41 USPQ2d 1217 (BPAI)(examiner has duty to supply factual basis for rejection); *In re Burt*, 365 F.2d 115, 148 USPQ 548 (CCPA 1966)(silence not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow). The required factual basis is lacking here. No attempt has been made to establish that HGH has these amino acids at these positions¹ and, therefore, there is no factual basis in the record for contending saccharose will stabilize anything other than HGH.

Moreover, no motivation for combining the references has been advanced. The fact that the references can be manipulated using hindsight does not satisfy the Examiner’s burden of establishing a prime facie case of obviousness. *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). That saccharose may stabilize HGH does not suggest it will stabilize something else, and particularly that it will stabilize GRF.

Faced with these deficiencies, the Final Rejection makes a series of assertions without citing any factual basis. Perhaps these are based on an unstated assertion of “common knowledge” but if so, that would be improper. *In re Lee*, *supra*. Nevertheless, each will now be considered.

¹ In actual fact, HGH does not have these amino acids at these positions -- the amino acid at the 3 position is Thr, at 4 is Ile, at 8 is Arg and at position 27 is Ser. See, e.g., US 6,348,444 at column 4, lines 40-46.

First, it is asserted that saccharose is a known “protein” stabilizer in the art and is known in the art as a stabilizer/preservative in “pharmaceutical formulations”. Even if the required factual basis was present, such broad and all encompassing statements about “proteins” and “pharmaceuticals” would not suggest use in connection with GRF. At the very best, these allegations would imply that saccharose might possibly be a stabilizer for proteins and that possibility should be explored. That, however, is application of an “obvious to try” standard which is improper and insufficient under Section 103.

Next, the Final Rejection avers that the present specification does not teach that saccharose will specifically denature or destabilize GRF nor were references cited to demonstrate this, leading to a conclusion that “there is no evidence that GRF would be expected to behave differently in saccharose [than in the absence of saccharose or in the presence of mannitol].” (Final Rejection, page 3, line 12-15). Since this averment is based on an expectation of no difference, any showing that there is a difference would be unexpected and establish the patentability of the instant invention. Such evidence is in the record and establishes that GRF plus saccharose acts in a different way than GRF or GRF plus the known stabilizer mannitol.

In this connection, the Board’s attention is respectfully invited to Tables 1 - 3 of the present application. Table formulations 1 and 2 contain mannitol while formulation 3 contains saccharose. Table 2 shows that with mannitol (formulations 1-2), the pH increased over the 4 weeks of the study whereas the formulation containing saccharose did not increase from the initial value. Table 3 shows that the peptide purity of the mannitol-containing compositions decreased by about 2% or more over the 4 weeks of the study whereas the saccharose-containing formulation lost only 0.2% over the same period of time. These results show that the formulation containing saccharose presented a better stability profile when compared to formulations

containing mannitol or mannitol combined with a phosphate buffer. Since mannitol is a known stabilizer for GRF, the stability of native GRF is necessarily inferior to the results achieved with mannitol present. The fact that saccharose provided a stability which is better than mannitol stabilized GRF is clearly surprising and unexpected when viewed in light of the conclusion in the Final Rejection that native (unstabilized) GRF or GRF stabilized with mannitol would be expected to have the same stability as a saccharose-containing composition. The claimed invention not only has a different stability, but the stability is greater than expected.

In an Advisory Action, the experimental results were dismissed on the grounds that amounts of saccharose and mannitol stabilizers compared differed. That Action, however, fails to recognize that saccharose and mannitol have different molecular weights so that one molecule of saccharose will weigh almost twice that of one molecule of mannitol. To compare the effect of two different materials as a stabilizer, the same number of mols should be used in each instance. The experiments reported in the application did so, using 0.1 mol of either saccharose or mannitol. The experimental results are valid and establish the unexpected results achieved by the invention.

Finally, the Final Rejection asserts there are no unexpected beneficial results or properties because saccharose is known in the art as a "preservative" and that the stability results in the specification are not greater than those which would have been expected from the prior art "to an unobvious extent." Even if the improper lack of a factual basis is ignored, the only "stability results . . . which would have been expected from the prior art" is that saccharose would have the same stability as achieved with mannitol stabilized GRF or native GRF (Final Rejection, page 3, lines 14-15). The factual data in the application discussed above shows that saccharose does cause a difference, a result which alone is unexpected relative to the expectation expressed in the Final

Rejection, and further that it improves stability to an extent which is clearly unexpected.

The rejection of claims 1-3, 6-10 and 13 is clearly untenable and should be reversed.

2. The Combination Of Fabbri, Samaritani and Fujioka
Fails to Make Claims 1, 4, 5, 11 And 12 Obvious

Claims 1, 4, 5, 11 and 12 have been rejected under 35 USC § 103 over Fabbri in view of Samaritani and Fujioka. Claim 1 is directed to a pharmaceutical composition comprising a solid intimate mixture of GRF and a stabilizing amount of saccharose, alone or in combination with other excipients such as buffering agents. The remaining claims subject to this rejection are in dependent form and specify amounts of GRF or of both GRF and saccharose.

The applicability of the combination Fabbri and Samaritani to the sole independent claim in this group (claim 1) has been discussed in the Section 1 above. All of the considerations discussed are also applicable here and will not be set forth again here.

The additional reference, Fujioka, does provide a teaching of a need for stabilization of GRF which was missing from the other references and does teach lyophilization of a composition containing 10 mg/vial of GRF. But neither of these teachings cures the basic deficiencies in the combination of Fabbri and Samaritani. Fujioka does not teach or suggest stabilizing GRF with saccharose and does not provide any factual basis for even trying some undisclosed material to determine if it might work. This rejection, like the rejection discussed earlier, does not even rise to the level of an obvious-to-try rejection. It should be reversed.

There is an additional consideration with respect to claims 5 and 12. These claims include the recitation of a specific amount of saccharose. No reason has been advanced as to why these amounts would be obvious. A prime facie basis for rejection of these claims is not present.

3. Fabbri Combined with Samaritani and Tarantino
Does Not Make Claims 1, 2, And 13-15 Obvious

Claims 1, 2 and 13-15 have been rejected under 35 USC § 103 over Fabbri in view of Samaritani and Tarantino. Claims 1 and 2 are directed to a pharmaceutical composition comprising a solid intimate mixture of GRF and a stabilizing amount of saccharose, alone or in combination with other excipients such as buffering agents. Claims 13-15 recite the additional presence of a buffer.

The applicability of the Fabbri and Samaritani combination to claims 1 and 2 have been discussed in the Argument Section 1 above and will not be repeated here. Tarantino does not cure the basic deficiency in this combination.

Tarantino relates to a composition for the sustained release of biologically active compounds which can be proteins or polypeptides including, inter alia, GRF. It indicates that the composition may contain stabilizers and specifically mentions human serum albumin, alpha-tocopherol and disodium EDTA. But no particular stabilizer is associated with GRF and indeed the reference states "these stabilizing substances will differ depending on the particular active ingredient that will be incorporated into composition." Col. 3, lines 48-51. There is no teaching or suggestion of the use of saccharose as a stabilizer for GRF or, for that matter, anything else, in this reference. Any composition containing saccharose as a stabilizer for GRF is unobvious over this three reference combination.

This rejection is untenable and should be reversed.

IX. CONCLUSION

None of the references, whether considered alone or in any combination, teach or suggest the use of saccharose to stabilize GRF, and such use provides an unexpected degree of stability. The claims on appeal should be allowed.

Dated: November 9, 2004

Respectfully submitted,

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APPENDIX A

1. A pharmaceutical composition comprising a solid intimate mixture of human growth releasing factor (GRF) and a stabilizing amount of saccharose, alone or in combination with other excipients.
2. The pharmaceutical composition according to Claim 1, wherein the solid intimate mixture is a lyophilizate.
3. The pharmaceutical composition according to claim 1, wherein the stabilizing agent is a saccharose alone.
4. The pharmaceutical composition according to claim 1, containing 3 or 10 mg/vial of hGRF.
5. The pharmaceutical composition according to claim 1 comprising 3 or 10 mg/vial of hGRF and 20.52 or 68.4 mg/vial of saccharose.
6. The pharmaceutical composition according to claim 1 further comprising buffering agents.
7. A process for preparing a pharmaceutical composition according to claim 1, comprising the preparation of an aqueous solution of the components, the distribution within containers and the lyophilization in the containers.
8. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to claim 1, hermetically closed in a sterile condition within a container suited for a storage before use and for reconstitution of the mixture into a solvent or into a solution for injectables.

9. A solution comprising the solid mixture according to claim 1, reconstituted in a solvent or a solution for injectables.

10. The pharmaceutical composition according to claim 2, wherein the stabilizing agent is a saccharose alone.

11. The pharmaceutical composition according to claim 2, containing 3 or 10 mg/vial of hGRF.

12. The pharmaceutical composition according to claim 1 comprising 3 or 10 mg/vial of hGRF and 20.52 to 68.4 mg/vial of saccharose.

13. The pharmaceutical composition according to claim 2 further comprising buffering agents.

14. The pharmaceutical composition according to claim 13 buffered to a pH between 2 and 7.

15. The pharmaceutical composition according to claim 14 buffered to a pH of 4 to 6.